IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVENTIS PHARMA S.A., SANOFI-AVENTIS U.S., LLC	)	
Plaintiffs,	)	Civil Action No. _____
v.	)	
APOTEX, INC., APOTEX CORP.,	)	
Defendants.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs, Aventis Pharma S.A., and sanofi-aventis U.S., LLC (collectively, "sanofi-aventis"), for their complaint against Defendants Apotex, Inc. and Apotex Corp. (collectively, "Apotex") hereby state as follows:

THE PARTIES

1. Aventis Pharma S.A. is a French corporation with its principal place of business in Paris, France. Sanofi-aventis U.S., LLC is a Delaware corporation with its principal place of business in Bridgewater, New Jersey.

2. Sanofi-aventis is in the business of developing, manufacturing, and selling a wide variety of consumer products, including pharmaceutical products. Sanofi-aventis U.S., LLC is the holder of approved New Drug Application No. 020-449 for the active ingredient docetaxel, which has the proprietary name Taxotere®. Taxotere® is sold by sanofi-aventis throughout the United States, and it has been approved by the FDA for seven indications. Worldwide,

Taxotere® is marketed in over 100 countries and used for the treatment of, among other things, breast, lung, prostate, gastric, and head and neck cancer.

3. Upon information and belief, Defendant Apotex, Inc. is a company organized and existing under the laws of Canada with a place of business at 150 Signet Drive, Toronto, Ontario, Canada M9l 1T9. Upon information and belief, Apotex, Inc. is a wholly owned subsidiary of Apotex Pharmaceutical Holdings Inc. Upon information and belief, Defendant Apotex, Inc. manufactures numerous generic drugs for sale and use throughout the United States, including this judicial district.

4. Upon information and belief, Apotex Inc. has availed itself of the legal protections of the State of Delaware, having filed counterclaims seeking judicial relief from this Court in, among other cases, *Sanofi-Aventis, et al v. Apotex Inc. et al*, Civil No. 07-792.

5. Upon information and belief, Defendant Apotex Corp. is a corporation organized and existing under the laws of Delaware with a place of business at 2400 North Commerce Parkway, Weston, Florida, 33326. Upon information and belief, Apotex Corp. is a wholly owned subsidiary of Apotex Pharmaceutical Holdings Inc. Apotex Corp. is registered to do business in Delaware and The Corporation Trust Company, Corporation Trust Center, 1209 Orange Street, Wilmington, Delaware, 19801, is its registered agent in Delaware.

6. Upon information and belief, Apotex Corp. has availed itself of the legal protections of the State of Delaware, having filed counterclaims seeking judicial relief from this Court in, among other cases, *Sanofi-Aventis, et al v. Apotex Inc. et al*, Civil No. 07-792. Apotex Corp. has also admitted to personal jurisdiction in this court in the aforementioned action.

NATURE OF THE ACTION

7. This is a civil action for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. § 100, et seq., and in particular under 35 U.S.C. § 271(e). This action relates to a New Drug Application ("NDA") filed by Apotex with the United States Food and Drug Administration ("FDA") for approval to market a copy of sanofi-aventis' highly successful Taxotere® pharmaceutical products that are sold in the United States.

JURISDICTION AND VENUE

8. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331 and 1338(a).

9. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious action of patent infringement that has led to foreseeable harm and injury to Plaintiffs, which manufacture numerous drugs for sale and use throughout the United States, including this judicial district. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

10. This court has personal jurisdiction over Defendant Apotex, Inc. by virtue of, *inter alia*, its systematic and continuous contacts with Delaware, including the substantial revenue it derives from the State of Delaware through its sister corporation and agent Apotex Corp, as well as its purposeful availment of this forum, such as its filing of claims and counterclaims in this jurisdiction.

11. This Court has personal jurisdiction over Defendant Apotex Corp. because it is incorporated under the laws of the State of Delaware, is registered to do business in the State of Delaware, and has a registered agent in the State of Delaware, and by virtue of, *inter alia*, its engaging in systematic and continuous contact with the State of Delaware, deriving substantial revenue from generic drugs consumed in the State of Delaware, as well as its purposeful availment of this forum, such as its filing of claims and counterclaims in this jurisdiction.

12. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(c) and 1400(b).

BACKGROUND

13. Upon information and belief, Defendants have filed with the FDA in Rockville, Maryland, New Drug Application 22-312 ("the Apotex NDA") under 21 U.S.C. § 355(b)(2) (also known as a 505(b)(2) application) to obtain FDA approval for the commercial manufacture, use, and sale of a docetaxel injection product in the following dosage forms: 40 mg/ml, 20 mg/0.5 ml and 80 mg/2ml. Apotex filed its NDA No. 22-312 to obtain approval to market a generic form of docetaxel injection solution, which is currently marketed by sanofi-aventis under the brand name Taxotere® (docetaxel) Injection Concentrate, before the expiration of certain sanofi-aventis patents, including U.S. Patent Nos. 5,438,072, 5,698,582, 5,714,512 and 5,750,561.

14. On behalf of Apotex, Bernice Tao, as Director of Regulatory Affairs US for Apotex, Inc., sent a letter dated June 27, 2008 to Plaintiffs to provide notice, pursuant to 21 U.S.C. § 355(b)(3)(B), that Apotex had filed NDA 22-312 with respect to docetaxel injection solution in a variety of dosage forms (40 mg/ml, 20 mg/0.5 ml and 80 mg/2ml). The letter further provided notice that Apotex had filed with the FDA, pursuant to 21 U.S.C.

§ 355(b)(2)(A)(iv), a certification ("Paragraph IV certification") alleging that U.S. Patent Nos. 4,814,470; 5,438,072; 5,698,582; 5,714,512; and 5,750,561 (collectively, "sanofi-aventis' patents") are invalid, not infringed, and/or not enforceable. The letter also included a statement of factual and legal allegations upon which Apotex based its certifications to the FDA.

APOTEX'S FAILURE TO COMPLY WITH ITS OFFER OF CONFIDENTIAL ACCESS

15. In a letter dated June 27, 2008, Apotex offered sanofi-aventis confidential access to the Apotex NDA. Its offer of confidential access permitted one outside law firm to have access to the Apotex NDA for the purpose of determining if U.S. Patent Nos. 5,438,072, 5,698,582, 5,714,512 and 5,750,561 had been infringed by Apotex.

16. Counsel for sanofi-aventis contacted Apotex on July 11, 2008 in an attempt to modify the offer of confidential access to allow for outside experts and one in-house counsel at sanofi-aventis to have access to the Apotex NDA.

17. Almost two weeks later, on July 23, 2008, Apotex responded by email to the July 11, 2008 letter and proposed further modifications to the offer that would have prohibited outside experts from having access to the Apotex NDA.

18. Counsel for sanofi-aventis responded to Apotex's July 23, 2008 email in a letter dated July 25, 2008, requesting that permission be given for one outside expert to review the Apotex NDA.

19. Apotex responded to sanofi-aventis on July 29, 2008 and allowed for an outside expert to have access to the Apotex NDA.

20. On July 30, 2008, counsel for sanofi-aventis accepted Apotex's terms and faxed a signed offer of confidential access to Apotex.

21. On Friday, August 1, 2008, counsel for sanofi-aventis contacted, by email and voicemail, Ms. Eiko Yap, assistant to Apotex Vice President for Global Intellectual Property, Shashank Upadhye, to request that a countersigned copy of the offer of confidential access and the Apotex NDA be produced to counsel for sanofi-aventis. In two email messages from that day, counsel for sanofi-aventis included copies of the offer of confidential access regarding the Apotex NDA as signed by counsel for sanofi-aventis.

22. Having not heard a response from Apotex, counsel from sanofi-aventis again contacted Ms. Yap by email on Monday, August 4, 2008, requesting production of a countersigned copy of the offer of confidential access and the Apotex NDA. In addition, counsel for sanofi-aventis contacted Mr. Upadhye directly by voicemail on the morning of August 4, 2008. In the email message to Ms. Yap from August 4, 2008, counsel for sanofi-aventis included a copy of the offer of confidential access regarding the Apotex NDA as signed by counsel for sanofi-aventis.

23. In a telephone call on the morning of August 5, 2008, Ms. Eiko Yap responded to counsel for sanofi-aventis and promised that the countersigned offer of confidential access and the Apotex NDA would be produced to counsel for sanofi-aventis as soon as possible.

24. In an email message from 11:29 PM on the night of August 5, 2008, Apotex Vice President for Global Intellectual Property, Shashank Upadhye, responded to the August 4, 2008 voicemail left by sanofi-aventis counsel and asserted that he would be unable to produce the countersigned offer of confidential access and the Apotex NDA because counsel had not specified a product name or molecule in his voicemail message from the morning of August 4, 2008.

25. Counsel for sanofi-aventis responded to Mr. Upadhye's August 5, 2008 message by an electronically delivered letter on August 6, 2008.

26. On the morning of August 8, 2008, on the eve of the expiration of the 45-day period for filing this action under the Hatch-Waxman Act and contemporaneous with the filing of this complaint, Apotex returned a countersigned offer of confidential access accompanied by 13 pages that purport to be a part of the Apotex NDA, which, in complete form, upon information and belief, runs into the many thousands of pages. Apotex's untimely and de minimis production of a portion of its NDA complies with neither its Offer of Confidential Access nor the requirements of 21 U.S.C. § 355(j).

FIRST COUNT FOR INFRINGEMENT OF UNITED STATES PATENT NO. 5,714,512

27. The allegations of the preceding paragraphs 1-26 are repeated, realleged, and incorporated herein by reference.

28. United States Patent No. 5,714,512 B1 ("the '512 patent"), entitled "New Compositions Containing Taxane Derivatives" was duly and legally issued by the United States Patent and Trademark Office on February 3, 1998. Aventis Pharma S.A. is the owner by assignment of the '512 patent and has the right to sue for infringement thereof. A true and correct copy of the '512 patent is attached as Exhibit A.

29. Upon information and belief, Apotex's Paragraph IV certification alleged that its docetaxel injection product will not infringe claims 2-5, 8-12, 18-23, 28-31, and 34-35 of the '512 patent. Upon information and belief, Apotex's Paragraph IV certification alleged that all claims of the '512 patent are invalid.

30. Under 35 U.S.C. § 271(e)(2)(A), Apotex's submission to the FDA of NDA No. 22-312 to obtain approval for the commercial manufacture, use, or sale of its docetaxel injection product before the expiration of the '512 patent constitutes infringement of one or more claims of the '512 patent.

31. Upon FDA approval of NDA No. 22-312, Apotex will infringe the '512 patent by making, using, offering to sell, selling, and/or importing the docetaxel injection product in the United States, and by actively inducing and contributing to infringement by others under 35 U.S.C. §§ 271(b) and (c), unless this Court orders that the effective date of any FDA approval of Apotex's NDA shall be no earlier than the expiration date of the '512 patent.

32. Upon information and belief, Apotex's docetaxel injection product, when offered for sale, sold, and/or imported, and then used as directed, would be used in a manner that would directly infringe at least one of the claims of the '512 patent.

33. Upon information and belief, the use of Apotex's docetaxel injection product constitutes a material part of at least one of the claims of the '512 patent; Apotex knows that its docetaxel injection product is especially made or adapted for use in a manner infringing at least one of the claims of the '512 patent; and Apotex's docetaxel injection product is not a staple article or commodity of commerce suitable for substantial non-infringing use.

34. Upon information and belief, the offering to sell, sale, and/or importation of Apotex's docetaxel product would contributorily infringe at least one of the claims of the '512 patent.

35. Upon information and belief, Apotex had knowledge of the '512 patent and, by its promotional activities and package insert for its docetaxel injection product, knows or should

know that it will actively aid and abet another's direct infringement of at least one of the claims of the '512 patent.

36. Upon information and belief, the offering to sell, sale, and/or importation of Apotex's docetaxel injection product would actively induce infringement of at least one of the claims of the '512 patent.

37. Sanofi-aventis will be substantially and irreparably harmed by Apotex's infringing activities unless those activities are enjoined by this Court. Sanofi-aventis has no adequate remedy at law.

SECOND COUNT FOR INFRINGEMENT OF UNITED STATES PATENT No. 5,750,561

38. The allegations of the preceding paragraphs 1-37 are repeated, realleged, and incorporated herein by reference.

39. United States Patent No. 5,750,561 B1 ("the '561 patent"), entitled "Compositions Containing Taxane Derivatives" was duly and legally issued by the United States Patent and Trademark Office on May 12, 1998. Aventis Pharma S.A. is the owner by assignment of the '561 patent and has the right to sue for infringement thereof. A true and correct copy of the '561 patent is attached as Exhibit B.

40. Upon information and belief, Apotex's Paragraph IV certification alleged that its docetaxel injection product will not infringe any claim of the '561 patent.

41. Under 35 U.S.C. § 271(e)(2)(A), Apotex's submission to the FDA of NDA No. 22-312 to obtain approval for the commercial manufacture, use, or sale of its docetaxel injection product before the expiration of the '561 patent constitutes infringement of one or more claims of the '561 patent.

42. Upon FDA approval of NDA No. 22-312, Apotex will infringe the '561 patent by making, using, offering to sell, selling, and/or importing the docetaxel injection product in the United States, and by actively inducing and contributing to infringement by others under 35 U.S.C. §§ 271(b) and (c), unless this Court orders that the effective date of any FDA approval of Apotex's NDA shall be no earlier than the expiration date of the '561 patent.

43. Upon information and belief, Apotex's docetaxel injection product, when offered for sale, sold, and/or imported, and then used as directed, would be used in a manner that would directly infringe at least one of the claims of the '561 patent.

44. Upon information and belief, the use of Apotex's docetaxel injection product constitutes a material part of at least one of the claims of the '561 patent; Apotex knows that its docetaxel injection product is especially made or adapted for use in a manner infringing at least one of the claims of the '561 patent; and Apotex's docetaxel injection product is not a staple article or commodity of commerce suitable for substantial non-infringing use.

45. Upon information and belief, the offering to sell, sale, and/or importation of Apotex's docetaxel product would contributorily infringe at least one of the claims of the '561 patent.

46. Upon information and belief, Apotex had knowledge of the '561 patent and, by its promotional activities and package insert for its docetaxel injection product, knows or should know that it will actively aid and abet another's direct infringement of at least one of the claims of the '561 patent.

47. Upon information and belief, the offering to sell, sale, and/or importation of Apotex's docetaxel injection product would actively induce infringement of at least one of the claims of the '561 patent.

48. Sanofi-aventis will be substantially and irreparably harmed by Apotex's infringing activities unless those activities are enjoined by this Court. Sanofi-aventis has no adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, sanofi-aventis respectfully requests that this Court enter judgment in its favor as follows:

(1) declaring that, under 35 U.S.C. § 271(e)(2)(A), Apotex's submission to the FDA of NDA No. 22-312 to obtain approval for the commercial manufacture, use, offer for sale, or sale in, or importation into, the United States of Apotex's docetaxel injection product before the expiration of the '512 patent was an act of infringement of the '512 patent;

(2) declaring that Apotex's commercial manufacture, use, offer for sale, or sale in, or importation into, the United States of Apotex's docetaxel injection product would constitute infringement of the '512 patent;

(3) declaring that, under 35 U.S.C. § 271(e)(2)(A), Apotex's submission to the FDA of NDA No. 22-312 to obtain approval for the commercial manufacture, use, offer for sale, or sale in, or importation into, the United States of Apotex's docetaxel injection product before the expiration of the '561 patent was an act of infringement of the '561 patent;

(4) declaring that Apotex's commercial manufacture, use, offer for sale, or sale in, or importation into, the United States of Apotex's docetaxel injection product would constitute infringement of the '561 patent;

(5) ordering that the effective date of any FDA approval of Apotex's docetaxel injection product shall be no earlier than the expiration of the '512 patent, in accordance with 35 U.S.C. § 271(e)(4)(A);

(6) ordering that the effective date of any FDA approval of Apotex's docetaxel injection product shall be no earlier than the expiration of the '561 patent, in accordance with 35 U.S.C. § 271(e)(4)(A);

(7) enjoining Apotex and all persons and entities acting in concert with Apotex from commercially manufacturing, using, offering for sale, or selling Apotex's docetaxel injection product within the United States, or importing Apotex's docetaxel injection product into the United States, until the expiration of the '512 patent, in accordance with 35 U.S.C. § 271(e)(4)(B);

(8) enjoining Apotex and all persons and entities acting in concert with Apotex from commercially manufacturing, using, offering for sale, or selling Apotex's docetaxel injection product within the United States, or importing Apotex's docetaxel injection product into the United States, until the expiration of the '561 patent, in accordance with 35 U.S.C. § 271(e)(4)(B);

(9) awarding sanofi-aventis its costs and expenses in this action; and awarding sanofi-aventis any further and additional relief as this Court deems just and proper.

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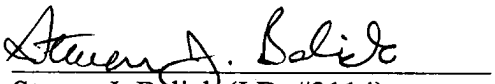

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Date: August 8, 2008

EXHIBIT A

US005714512A

United States Patent [19]

Bastart et al.

[11] **Patent Number: 5,714,512**

[45] **Date of Patent: Feb. 3, 1998**

[54] **NEW COMPOSITIONS CONTAINING TAXANE DERIVATIVES**

[75] Inventors: **Jean-Pierre Bastart**, Lesigny; **Thierry Dupechez**, Villemoisson Sur Orge; **Jean-Louis Fabre**, Paris, all of France

[73] Assignee: **Rhone-Poulenc Rorer, S.A.**, Antony Cedex, France

[21] Appl. No.: **568,760**

[22] Filed: **Dec. 7, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 398,011, Mar. 3, 1995, which is a continuation-in-part of Ser. No. 930,392, Aug. 23, 1993, Pat. No. 5,403,858.

[30] **Foreign Application Priority Data**

Jul. 8, 1991 [FR] France 91 08527

[51] **Int. Cl.**[6] **A61K 31/335**

[52] **U.S. Cl.** **514/449**; 549/510; 514/471; 424/502

[58] **Field of Search** 514/449; 424/502

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,206,221	6/1980	Miller et al.	424/278
4,960,790	10/1990	Stella et al.	514/449
5,403,858	4/1995	Bastart et al.	514/449

OTHER PUBLICATIONS

B.D. Tarr, "A New Parenteral Vehicle for the Administration of Some Poorly Water Soluble Anti-Cancer Drugs," J. Parenter. Sci. Technol., 41(1), 31-33 (1987).

Merck Index, 11th ed., #7559 (1989).

Primary Examiner—Amelia Owens

Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner

[57] **ABSTRACT**

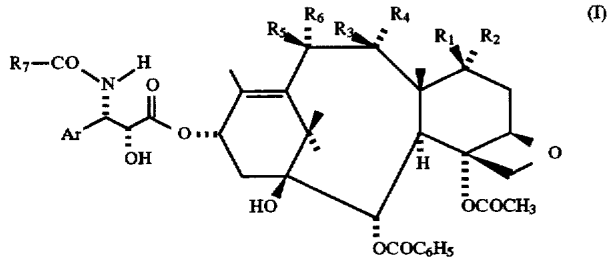
This invention relates to compositions containing taxane derivatives, consisting of a solution of such derivatives in a surfactant. These compositions can be used to prepare perfusion solutions.

35 Claims, No Drawings

NEW COMPOSITIONS CONTAINING TAXANE DERIVATIVES

This is a continuation-in-part of Ser. No. 08/398,011, filed Mar. 3, 1995, which is a continuation-in-part of Ser. No. 07/930,392, filed Aug. 23, 1993, now U.S. Pat. No. 5,403,858 a national phase application of PCT/FR92/00624, filed Jul. 3, 1992, hereby incorporated by reference.

The present invention relates to compositions and especially pharmaceutical dosage forms containing therapeutic agents having antitumor and antileukemic activity. It relates more especially to compositions suitable for injection containing taxane derivatives, such as, in particular, taxol or one of its analogues or derivatives of the formula (I)



(I)

in which R_1 and R_2 each represent a hydrogen atom or one of R_1 and R_2 represents a hydrogen atom and the other represents a hydroxy, acyloxy, or acylcarbonyloxy radical, or R_2 represents a hydrogen atom and R_1 forms a single bond together with the methyl carbon atom situated in the α position, so they can form together a cyclopropane ring, one of R_3 and R_4 represents a hydrogen atom and the other represents a hydroxy radical, or R_3 and R_4 taken together form a oxo radical, R_5 and R_6 each represent each a hydrogen atom or one of R_5 and R_6 represents a hydrogen atom and the other represents a hydroxy, acyloxy, acylcarbonyloxy or a alkoxymethylcarbonyloxy radical, or R_5 and R_6 taken together form a oxo radical, R_7 represents an alkoxy, alkenyloxy, cycloalkyloxy or phenyl radical and Ar represents an aryl radical or preferably a phenyl radical optionally substituted by one or several atoms or radicals identical or different and selected from halogen, alkyl, alkoxy, dialkylamino, acylamino, alkylcarbonylamino or trifluoromethyl, or a 5 membered heterocyclic radical with one or more identical or different heteroatoms chosen from nitrogen, oxygen or sulfur, it being understood that alkyl radicals are straight chain or branched chain and contain 1 to 8 carbon atoms and the alkenyl radicals contain 2 to 8 carbon atoms. In one embodiment, it is preferred that when R_2 is a hydrogen atom and R_1 is a hydroxy radical, R_3 and R_4 cannot be simultaneously an oxo radical when R_6 is a hydrogen atom, R_5 is a hydroxy or acetyloxy radical, R_7 is a t.butoxy or a phenyl radical and Ar is a phenyl radical.

Representative taxane derivatives of the formula (I) include the following wherein R_2 represents a hydrogen atom and R_1 represents a hydrogen atom or a hydroxy radical, or R_1 forms a single bond together with the methyl carbon atom situated in the α position, so they can form together a cyclopropane cycle, R_3 and R_4 taken together form an oxo radical, R_6 represents a hydrogen atom and R_5 represents a hydrogen atom or a hydroxy, acetyloxy or methoxyacetyloxy radical, or R_5 and R_6 taken together form an oxo radical, R_7 represents a t.butoxy or a phenyl radical and Ar is a phenyl radical. In one embodiment, it is preferred that when R_2 is a hydrogen atom and R_1 is a hydroxy radical, R_3 and R_4 cannot be simultaneously an oxo radical when R_5 is a hydrogen atom, R_6 is a hydroxy or acetyloxy radical, R_7 is a t.butoxy or a phenyl radical and Ar is a phenyl radical.

The preferred taxane derivatives encompassed by the general formula (I) include two compounds which are known by the name of TAXOL and the name TAXOTERE.

These products exhibit in vivo substantial activity against malignant tumors, which has enabled them to be studied in the treatment of diseases resistant to other anticancer therapies.

Unfortunately, these products possess such low solubility in water that it has been necessary to prepare formulations for injection containing surfactant and ethanol. Ethanol is the best solvent for dissolving compounds of formula (I).

For example, according to the publication by Rowinsky, Lorraine, Cazenave and Donebower which appeared in the Journal of the National Cancer Institute, vol. 82, No. 15, pages 1247–1259 on 1st Aug. 1990, a first solution, termed "stock solution", containing approximately 6 mg/ml of taxol in a solvent mixture composed of:

50% by volume of ethanol

50% by volume of Cremophor EL.;

is prepared. On injection, this solution is mixed with a perfusion fluid containing sodium chloride or dextrose (glucose). To obtain a mixture which is stable from both a physical standpoint and a chemical standpoint, the authors of this paper state that it is necessary to limit the concentration of active principle in the perfusion solution to concentrations of approximately 0.03 to 0.6 mg/ml (see above publication, page 1251, column 1, third paragraph).

Now, it is desirable to be able to inject sufficient doses of active principle; to this end, clinicians would like to inject concentrations of active principle of between approximately 0.3 and 1 mg/ml in the perfusion fluid; above these doses, anaphylactic shock phenomena which are difficult to control, due in the main to the Cremophor, are seen (see the publication by Rowinsky, page 1250, second column, last paragraph).

Still according to this publication, to obtain such concentrations (between 0.3 and 1 mg/ml), it is necessary to inject solutions containing, at the same time as the active principle, concentrations of each of the following compounds, ethanol and most especially Cremophor, of approximately 8 g per 100 ml of solution. Since the treatment often requires the administration of high doses of active principle, and since the concentration of the active principle, and since the concentration of the active principle in the solution is relatively low, the injection of a large volume has the effect of causing, in addition to anaphylactic manifestations, manifestations of alcohol poisoning during the treatment.

The present invention provides compositions that make it possible either to reduce the ethanol concentrations greatly, or to eliminate Cremophor and ethanol completely from the perfusions.

For this purpose, according to a first implementation of the present invention, a composition suitable for use as a stock solution is prepared, containing a compound of formula I as defined above dissolved in a surfactant which may be a polysorbate, e.g. as marketed under the name "Tween", a polyoxyethylated vegetable oil as marketed, e.g., under the name "Emulphor", polyethoxylated castor oil, also known as glycerol polyethyleneglycol ricinoleate, as marketed, e.g., under the name Cremophor preferably CREMOPHOR® EL, and virtually free from ethanol. CREMOPHOR® EL is a non-ionic solubilizer and emulsifier that can be obtained by reacting ethylene oxide with castor oil in a molar ratio of 35–40 mol ethylene oxide to 1 mol glyceride and is commercially available from BASF and has been assigned CAS Registry Number 61791-12-6. The main component of CREMOPHOR® EL is glycerol-polyethyleneglycol

ricinoleate, which together with fatty acid esters of polyethylene glycol, represents the hydrophobic part of the product. The smaller, hydrophilic part consists of polyethylene glycols and ethoxylated glycerol.

The stock solution may be prepared by dissolving the active principle in ethanol, which is the best biocompatible solvent for the taxane derivatives, and then gradually adding the surfactant. Solutions containing 10 to 100 mg/ml of active principle in a mixture containing approximately 50% of surfactant can be prepared in this manner. The ethanol is then completely, or almost completely, eliminated.

To prepare, according to the present invention, the solution having a low ethanol content, the taxane derivative is dissolved in ethanol, and the surfactant, which enables micelles to be formed in containing the taxane derivative encapsulated in the surfactant after dilution in an aqueous medium, is then added. The ethanol contained in this solution is then removed at least partially by evaporation under vacuum or by any other suitable means.

According to a second method of preparing the stock solution, the taxane derivative is dissolved directly in the surfactant. According to a preferred method, a solution of surfactant containing, in particular, 1 to 2% of ethanol is prepared, and the taxane derivative is added continuously to this solution with stirring, e.g. using a helical grinder or a centrifugal disintegrator. The presence of a small amount of ethanol provides several advantages: the medium possesses a lower viscosity, and the wetting of the powder and the final filtration of the solution are improved.

The stock solution, having a low ethanol content, preferably contains less than 5% of ethanol; still more preferably, it contains less than 2% of ethanol. This solution is stable and can contain up to 200 mg/ml, preferably up to 80 mg/ml, of active principle in the surfactant.

A stock solution of taxol possesses still more preferably a concentration of between 6 and 20 mg/ml of active principle in the surfactant. This solution can be mixed, in particular to provide a final concentration of between 0.1 and 1 mg per milliliter, with the perfusion fluid, which can be physiological saline or a glucose solution. Perfusion prepared from the above stock solutions having a low ethanol content contain still more preferably between 0.3 and 0.5 mg/ml of taxol and less than 1 ml/l of ethanol.

The taxol perfusion containing the active principle without ethanol possesses a physical stability of between 8 and about one hundred hours. Physical stability is understood to mean that the solution does not exhibit any visible precipitation after 8 to 10 hours of storage at room temperature.

A stock solution of Taxotere preferably possesses a concentration of between 20 and 80 mg/ml of active principle in the surfactant. This solution can be mixed, in particular to provide a final concentration of between 0.1 and 0.5 mg per milliliter, with the perfusion fluid, which can be a physiological saline or a glucose solution. Perfusion prepared from the above stock solutions having a low ethanol content contain still more preferably between 0.1 and 0.3 mg/ml of Taxotere; they preferably contain less than 15 ml/l of surfactant and less than 1 ml/l of ethanol.

The Taxotere perfusion containing the active principle without ethanol possesses a physical stability which can reach several months.

The taxol or Taxotere perfusions may be injected into humans at a predetermined flow rate depending on the amount of active principle it is desired to inject. The anaphylactic shock phenomena which were observed with the solutions of the prior can be avoided with these solutions.

Thus, these perfusion have made it possible to reduce, relative to the prior art, the amount of surfactant injected into humans by approximately 80% and the amount of ethanol by almost 100%.

The invention is illustrated by the following Examples.

COMPARATIVE EXAMPLE ACCORDING TO THE PRIOR ART

Taxol (0.180 g) is dissolved in ethanol (15 ml). The mixture is made to volume with Cremophor to obtain a solution (30 ml) which contains taxol (6 mg/ml).

This solution is diluted in a 5% glucose perfusion in a proportion of 1 mg/ml; the perfusion solution in a proportion of 1 mg/ml; the perfusion solution contains 87.7 ml/l of Cremophor and 87.7 ml/l of ethanol. The perfusion solution is stable for more than 21 hours.

EXAMPLES 1–7

Taxotere (32 g) is dissolved in absolute ethanol (340 ml) and Polysorbate 80 (830 g) is then added. The ethanol is evaporated off in a rotary evaporator at 30° C. at a pressure of 15 mmHg for 2 hours. The solution obtained is stable; it contains Taxotere (40 mg/ml).

After dilution is a 5% glucose perfusion solution at concentrations of 0.1, 0.3 and 0.5 mg/ml, the stability of the solutions obtained is observed.

The same method is reproduced using a solution containing Taxotere (60 mg/ml).

The same test is reproduced using taxol solutions containing taxol (12 and 20 mg/ml).

The results are shown in Table 1.

Product	Solvent	Stock solution concentration	Active principle in the perfusion	Surfactant in the perfusion	Ethanol in the perfusion	Stability
taxol	Polysorbate	20 mg/ml	1 mg/ml	50 ml/l	<0.3 ml/l	>8 H
taxol	Polysorbate	20 mg/ml	0.3 mg/ml	15 ml/l	<0.09 ml/l	>24 H
taxol	Polysorbate	12 mg/ml	1 mg/ml	83.3 ml/l	<0.5 ml/l	>48 H
Taxotere	Polysorbate	40 mg/ml	0.5 mg/ml	11.6 ml/l	0.09 ml/l	8 H–23 H
Taxotere	Polysorbate	40 mg/ml	0.3 mg/ml	6.0 ml/l	0.05 ml/l	8 H–23 H
Taxotere	Polysorbate	40 mg/ml	0.1 mg/ml	2.3 ml/l	0.02 ml/l	29 H–45 H
Taxotere	Polysorbate	60 mg/ml	0.1 mg/ml	1.5 ml/l	<0.01 ml/l	8 H–23 H

EXAMPLE 8

Into a stainless steel reactor, Taxotere (258 g) is introduced and dissolved in ethanol (2425 g) with mechanical stirring for 45 minutes. Polysorbate 80 (6156 g) is added and the mixture is homogenized with mechanical stirring for 15 minutes. The solution is transferred to a reactor and the alcohol is distilled off under a reduced pressure of 10 to 50 millibars (1000 to 5000 Pa), the temperature being main-

tained at between 18° and 28° C. The alcohol is stilled off until its content is less than 2%.

The solution obtained is filtered through a filter having a pore size of 0.2 μm. It contains:

ethanol (1.3%)

Taxotere (39.6 mg/ml).

After dilution to mg/ml in a perfusion bag containing 5% glucose, the solution is stable without apparent precipitation for a period of more than two months.

EXAMPLE 9

Taxotere (160 mg) or taxol (160 mg) is dissolved in a mixture (10 ml) of absolute ethanol (2 ml) and Cremophor EL(218) (8 ml), and the ethanol is evaporated off in a rotary evaporator at 30° C. at a pressure of 25 mmHg for three hours. The solutions obtained are stable. They contain 20 mg/ml of Taxotere or taxol. After dilution in a 5% glucose perfusion solution at concentrations of 0.1 and 0.5 mg/ml, precipitation is observed at between 30 and 95 hours.

EXAMPLE 10

Polysorbate 80 (275.5 g) and absolute ethanol (5.4 g) are placed in a 500-ml Erlenmeyer flask, and the mixture is then stirred with a bar magnet until completely homogenized.

The solution prepared above (26.13 g) in a 50 ml flask, placed in a water bath heated beforehand and maintained throughout the test period at 30° C., is stirred at approximately 600 rpm with a bar magnet. With a spatula, Taxotere (1.076 g) is added in several portions so that the clumps disappear between two additions (the duration of the operation is approximately one hour). After incorporation of the last fraction of Taxotere, stirring is maintained until the solution becomes clear (approximately two hours).

EXAMPLE 11

4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl 3-t-butoxycarbonylamino-3-(2-fluorophenyl)-2-hydroxy-(2R, 3S)-propionate (20 mg) is placed in round bottom flask and dissolved in absolute ethanol (0.4 ml). After dissolution, polysorbate 80 (0.5 ml) is added and the mixture is homogenized with the aid of a magnetic stirrer. The flask is placed in a vacuum using a rotary evaporator and the alcohol is distilled off under reduced pressure (10 mmHg) for one hour. The solution obtained is perfectly clear and contains 40 mg/ml of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl 3-t-butoxycarbonylamino-3-(2-fluorophenyl)-2-hydroxy-(2R, 3S)-propionate. After dilution in a 0.9% aqueous sodium chloride perfusion solution to a concentration of 1 mg/ml, the solution obtained is stable for more than 24 hours.

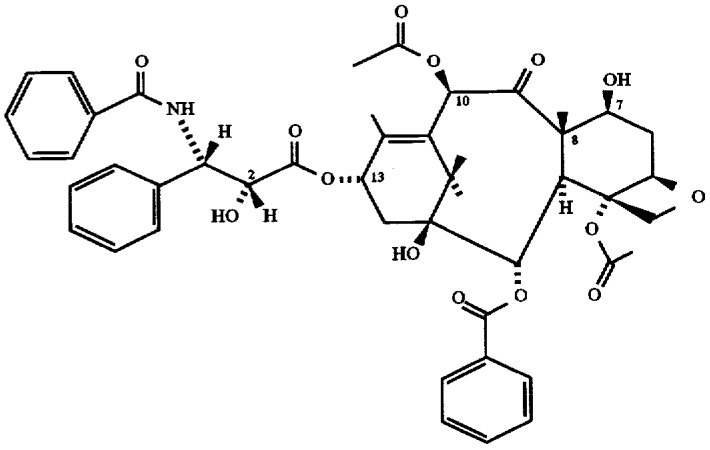
EXAMPLE 12

4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl 3-t-butoxycarbonylamino-3-(4-chlorophenyl)-2-hydroxy-(2R, 3S)-propionate (20 mg) was placed in a round bottomed flask and dissolved in absolute ethanol (0.4 ml). After dissolution, polysorbate 80 (0.5 ml) was added and the mixture was homogenized with the aid of magnetic stirrer. The flask was placed in a vacuum using a rotary evaporator and the alcohol was distilled off under reduced pressure (10 mmHg) for one hour. The solution obtained is perfectly clear and contains 40 mg/ml of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl 3-t-butoxycarbonylamino-3-(4-chlorophenyl)-2-hydroxy-(2R, 3S)-propionate. After dilution in a 0.9% aqueous sodium chloride perfusion solution to a concentration of 1 mg/ml, the solution obtained was stable for more than 24 hours.

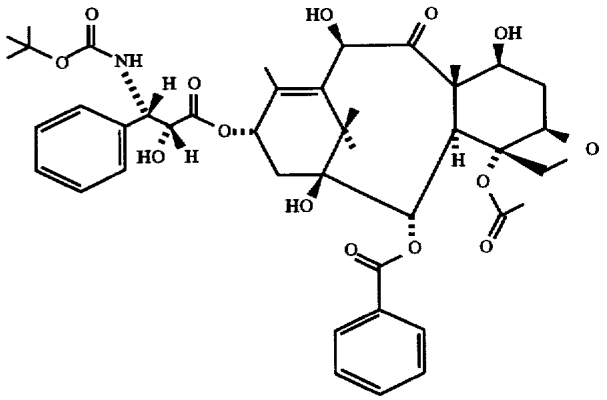
EXAMPLE 13

4α,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,8β-methylene-9 -oxo-19-nor-11-taxen-13α-yl 3-t-butoxycarbonylamino-2-hydroxy-3-phenyl-2-(2R,3S)-propionate (20 mg) was placed in a round bottomed flask and dissolved in absolute ethanol (0.4 ml). After dissolution, polysorbate 80 (0.5 ml) was added and the mixture was homogenized with the aid of a magnetic stirrer. The flask was placed in a vacuum using a rotary evaporator and the alcohol was distilled off under reduced pressure (10 mmHg) for one hour. The solution obtained is perfectly clear and contains 40 mg/ml of 4α,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,8β-methylene-9-oxo-19-nor-11-taxen-13α-yl 3-t-butoxycarbonylamino-2-hydroxy-3-phenyl-(2R,3S)-propionate. After dilution in a 0.9% aqueous sodium chloride perfusion solution to a concentration of 1 mg/ml, the solution obtained was stable for more than 24 hours.

TAXOL is the compound of formula I in which Ar is unsubstituted phenyl, R_7 is phenyl, R_5 is acetyloxy, R_6 is hydrogen, R_3 and R_4 taken together form an oxo radical, R_1 is hydroxy, and R_2 is hydrogen, as shown below:

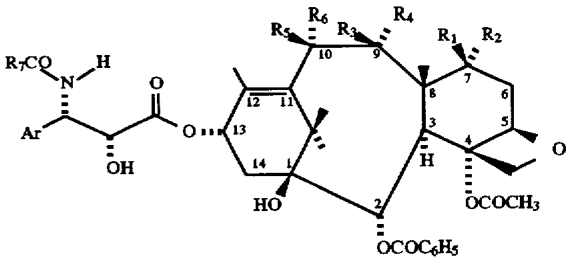


TAXOTERE is the compound of formula I in which Ar is unsubstituted phenyl, R_7 is t.butoxy, R_5 is hydroxy, R_6 is hydrogen, R_3 and R_4 taken together form an oxo radical, R_1 is hydroxy and R_2 is hydrogen, as shown below:



We claim:

1. A composition comprising a compound of the formula (I)



(I)

in which Ar is unsubstituted phenyl, R_7 is phenyl or t.butoxy, R_6 is hydrogen, R_5 is acetyloxy or hydroxy, R_3 and R_4 taken together form an oxo radical, R_1 is hydroxy and R_2 is hydrogen, said composition being dissolved in a surfactant selected from polysorbate, polyoxyethylated vegetable oil, and polyethoxylated castor oil, said composition being essentially free or free of ethanol.

2. The composition of claim 1, wherein R_5 is acetyloxy and R_7 is phenyl.

3. The composition of claim 2, wherein said surfactant is polysorbate.

4. The composition of claim 2, wherein said surfactant is polyoxyethylated vegetable oil.

5. The composition of claim 2, wherein said surfactant is polyethoxylated castor oil.

6. The composition of claim 1, wherein R_5 is hydroxy and R_7 is t.butoxy.

7. The composition of claim 6, wherein said surfactant is polysorbate.

8. The composition of claim 6, wherein said surfactant is polyoxyethylated vegetable oil.

9. The composition of claim 6, wherein said surfactant is polyethoxylated castor oil.

10. The composition of claim 1, said composition being a stock solution containing less than 5 volume % ethanol.

11. The composition of claim 10, said composition containing less than 2 volume % ethanol.

12. The composition of claim 10, said composition containing from 1 to 2 volume % ethanol.

13. The composition of claim 1, said composition containing up to 200 mg/ml of the compound of formula (I).

14. The composition of claim 13, said composition containing from 10 to 80 mg/ml of the compound of formula (I).

15. The composition of claim 14, said composition containing from 20 to 80 mg/ml of the compound of formula (I).

16. The composition of claim 13, said composition containing from 6 to 20 mg/ml of the compound of formula (I).

17. The composition of claim 13, said composition containing up to 80 mg/ml of the compound of formula (I).

18. The composition of claim 1, said composition being a perfusion containing less than 0.5 mg/ml of said compound of formula (I), less than 1 ml/l of said ethanol, and less than 15 ml/l of said surfactant.

19. The composition of claim 1, said composition being a perfusion containing less than 1 mg/ml of said compound of formula (I), and less than 1 ml/l of said ethanol.

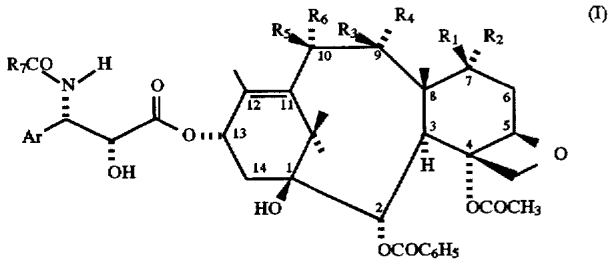
20. The composition of claim 2, said composition being a perfusion containing 0.1 to 0.3 mg/ml of said compound of formula (I).

21. A method for preparing a composition according to claim 1, which comprises dissolving said compound of formula (I) in ethanol, adding said surfactant and removing said ethanol.

22. The method of claim 21, wherein said ethanol is removed by evaporation.

23. A method for preparing a composition according to claim 1, which comprises slowly adding said compound of formula (I) to a solution of the surfactant containing 1 to 2 volume % ethanol.

24. A stock solution comprising a compound of the formula (I)



(I)

in which Ar is unsubstituted phenyl, R_7 is phenyl or t.butoxy, R_6 is hydrogen, R_5 is acetyloxy or hydroxy, R_3 and R_4 taken together form an oxo radical, R_1 is hydroxy and R_2 is hydrogen, said compound being dissolved in a surfactant selected from polysorbate, polyoxyethylated vegetable oil, and polyethoxylated castor oil, wherein said stock solution contains from 10 to 200 mg/ml of said compound of formula (I).

25. The stock solution of claim **24**, wherein said stock solution contains from 10 to 80 mg/ml of said compound of formula (I).

26. The stock solution of claim **25**, wherein said stock solution contains from 12 to 80 mg/ml of said compound of formula (I).

27. The stock solution of claim **26**, wherein said stock solution contains from 20 to 80 mg/ml of said compound of formula (I).

28. The stock solution of claim **24**, wherein R_5 is acetyloxy and R_7 is phenyl.

29. The stock solution of claim **28**, wherein said surfactant is polysorbate.

30. The stock solution of claim **28**, wherein said surfactant is polyoxyethylated vegetable oil.

31. The stock solution of claim **28**, wherein said surfactant is polyethoxylated castor oil.

32. The stock solution of claim **24**, wherein R_5 is hydroxy and R_7 is t.butoxy.

33. The stock solution of claim **32**, wherein said surfactant is polysorbate.

34. The stock solution of claim **32**, wherein said surfactant is polyoxyethylated vegetable oil.

35. The stock solution of claim **32**, wherein said surfactant is polyethoxylated castor oil.

* * * * *

EXHIBIT B

US005750561A

United States Patent [19]

Bastart et al.

[11] **Patent Number: 5,750,561**

[45] **Date of Patent: *May 12, 1998**

[54] **COMPOSITIONS CONTAINING TAXANE DERIVATIVES**

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[73] Assignee: **Rhone-Poulenc Rorer, S.A.**, Antony Cedex, France

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,403,858.

[21] Appl. No.: **422,672**

[22] Filed: **Apr. 12, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 930,393, Aug. 4, 1993, abandoned.

[30] **Foreign Application Priority Data**

Jul. 8, 1991 [FR] France 9108527

[51] **Int. Cl.**[6] **A61K 31/335**; A61K 31/34; A61K 9/50

[52] **U.S. Cl.** **514/449**; 514/471; 514/408; 424/502

[58] **Field of Search** 514/449, 471, 514/408; 424/502

[56] **References Cited**

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Primary Examiner—Theodore J. Criares

Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

[57] **ABSTRACT**

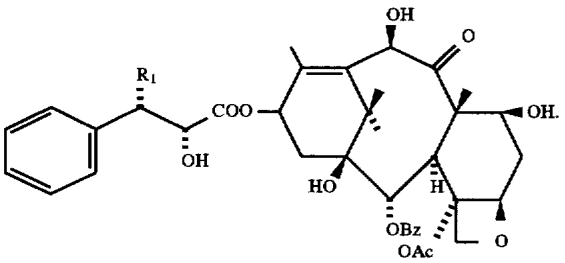
The invention provides new compositions containing taxane derivatives, consisting of solutions of such derivatives in a solvent mixture composed of ethanol and polysorbate. These compositions are used to prepare perfusions.

11 Claims, No Drawings

COMPOSITIONS CONTAINING TAXANE DERIVATIVES

This is a continuation of application Ser. No. 07/930,393, filed on Aug. 4, 1993, now abandoned.

The present invention relates to compositions containing therapeutic agents having antitumour and antileukaemic activity. It relates more especially to pharmaceutical, and in particular injectable, dosage forms containing taxane derivatives, such as, in particular, taxol or one of its analogues or derivatives of the following general formula:



(I)

Wherein R represents a hydrogen atom or an acetyl radical and R_1 represents a tert-butoxycarbonylamino or benzoylamino radical. The two derivatives in which R represents an acetyl group and R_1 a benzoylamino group or in which R represents a hydrogen atom and R_1 a tert-butoxycarbonylamino radical are preferred. The first of these two compounds is better known by the name of taxol, and the second is known by the name of Taxotere.

These products exhibit in vivo substantial activity against malignant tumours, which has enabled them to be studied in the treatment of diseases resistant to other anticancer therapies.

Unfortunately, these products possess such low solubility in water that it has been necessary to prepare a formulation for an injectable preparation based on surfactant and ethanol. Ethanol is the best solvent for dissolving compounds of the formula (I).

As an example, according to the publication by Rowinsky, Lorraine, Cazenave and Donehower which appeared in the Journal of the National Cancer Institute, vol. 82, No. 15, pages 1247–1259 on 1st Aug. 1990, a first solution, termed "stock solution", containing approximately 6 mg/ml of taxol in a solvent mixture composed of:

50% by volume of ethanol

50% by volume of Cremophor EL,

is prepared. For injection, this solution is mixed with a perfusion fluid containing sodium chloride or dextrose. To obtain a mixture which is stable from both a physical standpoint and a chemical standpoint, the authors of this paper state that it is necessary to limit the concentration of active principle in the perfusion solution to concentrations of approximately 0.03 to 0.6 mg/ml (see above publication, page 1251, column 1, third paragraph).

Now, it is desirable to be able to inject sufficient doses of active principle; to this end, clinicians would like to inject concentrations of active principle of between approximately 0.3 and 1 mg/ml in the perfusion fluid; above these doses, anaphylactic shock phenomena which are difficult to control, due in the main to the Cremophor, are seen (see the publication by Rowinsky, page 1250, second column, last paragraph).

This publication also discloses that, to obtain such concentrations (between 0.3 and 1 mg/ml), it is necessary to inject solutions containing, as well as the active principle, concentrations of each of the following compounds, ethanol and most especially Cremophor, of approximately 8 g per 100 ml of solution. Since the treatment often requires the administration of high doses of active principle, and since the concentration of the active principle in the solution is relatively low, the injection of a large volume has the effect of causing, in addition to anaphylactic manifestations, manifestations of alcohol intoxication during the treatment.

It has been discovered that, by the use of the pharmaceutical dosage forms of the present invention, it is possible to avoid the use of Cremophor and greatly to reduce the ethanol concentrations used.

For this purpose, a stock solution is prepared, containing the active principle of formula I in a solvent mixture composed of ethanol, which is the best biocompatible solvent for active principles of this class, and a polysorbate surfactant, e.g. as marketed, in particular, under the name "Tween".

The stock solution is prepared by dissolving the active principle in ethanol and then gradually adding the surfactant. Solutions containing 10 to 100 mg/ml of active principle in a mixture containing approximately 50% of surfactant can be prepared in this manner.

The present invention then makes it possible to replace the Cremophor, described in the publication of the Journal of National Cancer Institute, by a polysorbate. In effect, when an injectable solution containing ethanol and a polysorbate 80 surfactant in place of Cremophor was used in the clinical situation, it became apparent that the anaphylactic reactions were greatly reduced compared with the use of the same solution prepared with Cremophor. In addition to this considerable advantage, it became apparent, most surprisingly, that, in the bottles of stock solution, the concentration of active principle can reach 15 mg/ml. The perfusion fluid after dilution of these bottles contains an amount of ethanol, and also an amount of surfactant, which is reduced a little over twofold.

The perfusions prepared from the above stock solutions, and containing a concentration of active principle of, e.g., 1 mg/ml, which is a preference, or less, contain less than 50 ml/l and preferably less than 35 ml/l of surfactant and of ethanol, which represents a reduction of approximately 40% relative to the perfusions of the prior art.

The new perfusions are stable from a physical standpoint, that is to say no precipitation phenomenon is seen to appear within approximately 8 hours.

The taxol or Taxotere perfusions may be injected into humans at a predetermined flow rate depending on the amount of active principle it is desired to inject. The anaphylactic shock phenomena which were observed with the solutions of the prior art are not observed with these solutions.

The invention is described more completely in the Examples which follow, which are not to be considered as limiting the invention.

EXAMPLES ACCORDING TO THE INVENTION

EXAMPLE 1

Taxotere (0.450 g) is dissolved in ethanol (15 ml). The mixture is made to 30 ml with polysorbate 80 to obtain a solution containing Taxotere (15 mg/ml). The physicochemical stability of this solution is satisfactory.

After mixing with a 5% glucose solution so as to obtain a final concentration of 1 mg/ml, this solution contains 33 ml/l of polysorbate 80 and 33 ml/l of ethanol.

The perfusion is stable for more than 21 hours, i.e. no precipitation phenomenon is seen during this period.

EXAMPLE 2

Example 1 is reproduced with an initial concentration of 10 mg/ml of Taxotere; the results are shown in Table 1.

COMPARATIVE EXAMPLE ACCORDING TO THE PRIOR ART

Taxol (0.180 g) is dissolved in ethanol (15 ml). The mixture is made to volume with Cremophor to obtain a solution (30 ml) which contains taxol (6 mg/ml).

This solution is diluted in the same perfusion solution as above to five a final concentration of 1 mg/ml; the perfusion solution contains 87.7 ml/l of Cremophor and 87.7 ml/l of ethanol. The perfusion solution is stable for more than 21 hours.

EXAMPLE 3

Taxotere (65 g) is dissolved in ethanol (2083 ml). The volume is adjusted to 4147 ml by adding polysorbate 80 (2083 ml). The mixture is homogenised by mechanical stirring. It is filtered through a filter of pore size 0.2 µm. A solution containing Taxotere (approximately 15 mg/ml) is obtained.

After dilution to a Taxotere content of 1 mg/ml in a perfusion bag containing 5% dextrose, this solution is stable for at least 96 hours.

5. A perfusion, which contains approximately 1 mg/ml or less of compound of formula as defined in claim 1, and which contains less than 35 ml/l of ethanol and less than 35 ml/l of polysorbate, wherein said perfusion is capable of being injected without anaphylactic or alcohol intoxication manifestations being associated therewith.

6. A stock solution consisting essentially of a mixture of taxotere and ethanol in a ratio of about 3:100 by weight, and an amount of polysorbate to provide a solution containing about 10 to 15 mg/ml of taxotere, whereby said stock solution is used to form an injectable solution which contains up to about 1 mg/ml of the compound of formula as defined in claim 1, said injectable solution being capable of being injected without anaphylactic or alcohol intoxication manifestations being associated herewith.

7. A perfusion consisting essentially of the stock solution of claim 6 and an amount of glucose solution or dextrose solution to obtain a solution containing about 1 mg/ml of taxotere.

8. A therapeutic composition consisting essentially of a taxane derivative dissolved in a mixture of ethanol and a polysorbate, whereby said therapeutic composition forms or is used to form an injectable solution which contains up to about 1 mg/ml of the compound of formula as defined in claim 1, said injectable solution being capable of being injected without anaphylactic or alcohol intoxication manifestations being associated herewith.

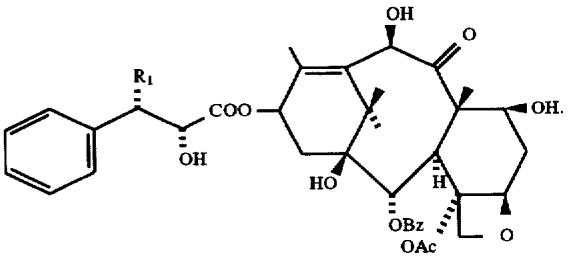
9. The composition of claim 8 wherein said taxane derivative is taxol or an analogue or derivative thereof.

TABLE 1

Example	Product	Solvent	Stock solution concentration	Active principle in the perfusion	Surfactant in the perfusion	Ethanol in the perfusion	Stability
Comparative	taxol	EtOH/Crem	6 mg/ml	1 mg/ml	87.7 ml/l	87.7 ml/l	>21 H
	taxol	EtOH/Poly	6 mg/ml	1 mg/ml	83.3 ml/l	83.3 ml/l	>21 H
1	Taxotere	EtOH/Poly	15 mg/ml	1 mg/ml	33.3 ml/l	33.3 ml/l	>21 H
2	Taxotere	EtOH/Poly	10 mg/ml	1 mg/ml	50 ml/l	50 ml/l	>21 H

We claim:

1. A composition consisting essentially of a compound of formula:



(I)

in which R represents a hydrogen atom or an acetyl radical and R_1 represents a tert-butoxycarbonylamino or benzoylamino radical, dissolved in a mixture of ethanol and a polysorbate whereby said composition is used to form an injectable solution which contains up to about 1 mg/ml of the compound of formula I, said injectable solution being capable of being injected without anaphylactic or alcohol intoxication manifestations being associated therewith.

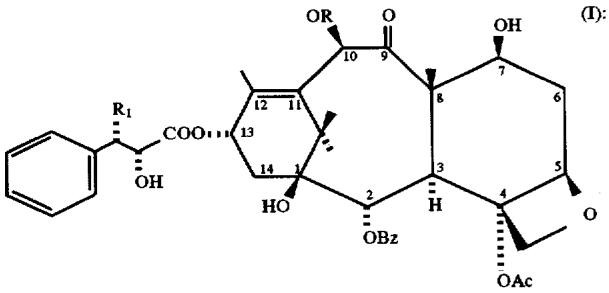
2. A composition according to claim 1, wherein, in the compound of formula (I), R represents a hydrogen atom and R_1 represents a tert-butoxycarbonylamino radical.

3. A composition according to claim 1, wherein, in the compound of formula (I), R represents an acetyl group and R_1 represents a benzoylamino radical.

4. A composition according to claim 1, which contains between 6 and 15 mg/ml of compound of formula (I).

10. The composition of claim 8 wherein said taxane derivative is taxotere or an analogue or derivative thereof.

11. A composition consisting essentially of a compound of formula



(I):

in which R represents a hydrogen atom or an acetyl radical and R_1 represents a tert-butoxycarbonylamino or benzoylamino radical,

dissolved in a mixture of ethanol and polysorbate, wherein said ethanol is present in an amount of less than 5% and said polysorbate is present in an amount of less than 5%, said composition being used to form an injectable solution capable of being injected without anaphylactic or alcohol intoxication manifestations being associated herewith.

* * * * *

JS 44 (Rev. 12/07)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

AVENTIS PHARMA S.A., and
SANOFI-AVENTIS U.S., LLC

(b) County of Residence of First Listed Plaintiff *
(EXCEPT IN U.S. PLAINTIFF CASES)

* First-listed plaintiff is a French corporation

(c) Attorney's (Firm Name, Address, and Telephone Number)
Steven J. Balick, ASHBY & GEDDES, 500 Delaware Ave., P.O. Box 1150, Wilmington, DE 19899 (302) 654-1888

DEFENDANTS

APOTEX, INC., and APOTEX CORP.

County of Residence of First Listed Defendant
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

Unknown

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 463 Habeas Corpus - Alien Detainee
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity)**:
35 U.S. Code section 100, et seq

Brief description of cause:
Action arising under the patent laws of the United States

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE Gregory M. Sleet DOCKET NUMBER 07-721-GMS

DATE
August 8, 2008

SIGNATURE OF ATTORNEY OF RECORD
Steven J. Balick

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 08 496

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 2 COPIES OF AO FORM 85.

8/8/08
(Date forms issued)

X [signature]
(Signature of Party or their Representative)

X Marcus Robinson
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action